

NOTES

MUCOPOLYSACCHARIDOSIS

GENERALLY, WHAT IS IT?

PATHOLOGY & CAUSES

- **Metabolic disorder:** dysfunction of lysosomal enzymes involved in glycosaminoglycans (GAG) breakdown
- Lysosomal storage disease
- Impaired glycosaminoglycans metabolism → GAGs (heparan, dermatan, keratan, chondroitin sulfate) accumulation within lysosomes → damage of cells, tissues, organs
 - **Heparan (in nervous tissue):** decline of neurological function
 - **Keratan (in skeletal system):** skeletal abnormalities
 - **Dermatan (in skin, lungs, heart valves):** skin changes, mitral valve damage, lung diseases

TYPES

MPS I: Hurler syndrome

- Attenuated MPS I
- Severe MPS I
 - Associated with progressive intellectual disability, earlier onset

MPS II: Hunter syndrome

- Mild to severe forms

MPS III: Sanfilippo syndrome

- **Four forms:** A, B, C, D
- Early life clinical presentation
- Lack of appropriate enzymes → accumulation heparan sulfate → neurological damage → adolescent death

MPS IV: Morquio syndrome

- **Two forms:** A, B
- Keratan, chondroitin sulfate accumulation

- Residual enzyme activity determines life expectancy

MPS VI: Maroteaux-Lamy syndrome

- Dermatan, chondroitin sulfate accumulation
- Mild to severe forms

MPS VII: Sly syndrome

- Heparan, dermatan, chondroitin sulfate accumulation
- Mild to severe forms

MPS IX: Natowicz syndrome (rarest type)

- Hyaluronidase deficit → hyaluronan accumulation

CAUSES

- Inherited autosomal recessive, except for MPS II (X-linked)

COMPLICATIONS

- Hearing, vision loss
- Skeletal abnormalities, limited movement
- Valve dysfunction
- Recurrent respiratory infections
- Joint stiffness
- Behavioral problems, intellectual disability
- C1-C2 subluxation → cord compression → central apnea
- Hydrocephalus

SIGNS & SYMPTOMS

MPS III: Sanfilippo syndrome

- Three stages
 - Mental, motor skills delays (usually between ages two–six)
 - Sleep disorders, hyperactivity with aggressiveness, dementia
 - Inability to walk until age of ten

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- Visual, hearing problems; CNS degeneration; intellectual disability; excessive hair growth

MPS IV: Morquio syndrome

- Skeletal abnormalities, joint stiffness, blurry cornea, common ear infections, hearing loss, breathing difficulties
- **Severe forms:** life expectancy of four decades
- **Mild forms:** life expectancy up to seven decades

MPS VI: Maroteaux-Lamy syndrome

- Large head, tongue; rough facial features; corneal cloudiness; heart, hearing problems; short growth; progressive, limiting skeletal disorders; spinal cord damage from spinal stenosis
- **Mild form:** slower progression

MPS VII: Sly syndrome

- Hydrops fetalis; skeletal, soft tissue abnormalities

MPS IX: Natowicz syndrome

- Pain, swelling nodular masses of soft tissue around joints

DIAGNOSIS

DIAGNOSTIC IMAGING

CT scan/MRI

- **Maroteaux-Lamy:** spinal canal stenosis, cord compression

X-ray

- **Sanfilippo syndrome:** dysostosis multiplex
- **Morquio syndrome:** dysostosis multiplex, vertebra flattening, pectus carinatum, odontoid dysplasia
- **Sly syndrome:** flared ribs, pectus carinatum

LAB RESULTS

- **Prenatal diagnosis:** enzyme activity measurement in amniotic cells
- **Enzyme test:** ↓ activity

Urine analysis

- ↑ glycosaminoglycans
 - **Sanfilippo syndrome:** ↑ heparan sulfate
 - **Morquio syndrome:** ↑ keratan sulfate
 - **Maroteaux-Lamy syndrome:** ↑ dermatan sulfate
 - **Sly syndrome:** ↑ dermatan, heparan sulfate

TREATMENT

OTHER INTERVENTIONS

- No definitive cure
- Enzyme replacement therapy
- Hematopoietic bone marrow transplant
- Home exercises
- Gene therapy in development
- Treat associated complications

HUNTER SYNDROME

osms.it/hunter-syndrome

PATHOLOGY & CAUSES

- X-linked disorder
 - Impaired metabolism of glycosaminoglycans (GAG) → heparan, dermatan sulfate accumulation

TYPES

MPS II A (severe form)

- Affects children in early life

MPS II B (mild form)

- Symptoms later in life; life expectancy up to seventy years

CAUSES

- Mutation of *IDS* gene → enzyme iduronate-2-sulfatase dysfunction → ineffective breakdown of GAG in lysosomes → accumulation; cell, tissue, organ damage

COMPLICATIONS

MPS II A

- Carpal tunnel syndrome
- Airway obstruction
- Heart problems
 - Heart valve leaflet dysfunction; thickening of the myocardium → coronary blood vessel compression
- Intellectual disability
- Seizures

MPS II B

- Valvular heart disease, hydrocephalus

SIGNS & SYMPTOMS

- Death due to heart and lung problems
- Lack of blurry cornea differentiates Hunter syndrome from Hurler syndrome

MPS II A

- Early life
 - Rough facial features (enlarged head, flat bridge of nose, bulging forehead)
 - Skeletal abnormalities, stiff joints, limited movement
 - Intellectual disability
 - Skin (ivory colored lesions)
- Later life
 - Progressive neurological decline
 - Hydrocephalus
 - Seizures

MPS II B

- Later onset: milder symptoms
- Rough facial features
- Rigid joints
- Hearing, pulmonary disorders

DIAGNOSIS

DIAGNOSTIC IMAGING

X-ray

- Skeletal abnormalities

CT scan/MRI

- Cord compression level, odontoid hypoplasia assessment

LAB RESULTS

- Prenatal diagnosis
 - ↓ enzyme activity in amniocytes
- Enzyme-linked immunosorbent assay (ELISA)
 - ↑ heparan, dermatan sulfate in blood, urine
- Enzyme activity test on leucocytes/fibroblasts
 - ↓ activity
- Bone marrow cells histology
 - Alder-Reilly granulations

OTHER DIAGNOSTICS

- Physical examination
 - Characteristic findings

ECG, pulmonary testing

- Determination of functions

TREATMENT

OTHER INTERVENTIONS

- No definitive cure
- Address complications
- Recombinant human iduronate sulfatase
 - dursulfase; enzyme replacement therapy
- Hematopoietic bone marrow transplant

HURLER SYNDROME (MPS I)

osms.it/hurler-syndrome

PATHOLOGY & CAUSES

- Autosomal recessive disorder; glycosaminoglycans buildup
- Alpha-L iduronidase deficiency → heparan sulfate accumulation in lysosomes → cell, tissue, organ damage

TYPES

Attenuated form

- Better prognosis
- Presentation: age two–adolescence
- Life expectancy: twenties–middle age

Severe form

- Presentation: within first two years
- Life expectancy: about 10 years

CAUSES

- IDUA gene mutation

COMPLICATIONS

- Carpal tunnel syndrome
- Heart valve abnormalities → heart failure
- Thick secretions → frequent sinopulmonary infections
- Enlargement of tonsils, adenoids → airway obstruction → sleep apnea
- Vision, hearing loss

- C1-C2 subluxation → spinal cord compression → central apnea
- Hydrocephalus

SIGNS & SYMPTOMS

- Developmental delays; in severe form, progressive intellectual disability
- Attenuated form; normal intelligence
- Rough facial features
 - Enlarged head, nose, cheeks, lips, tongue
- Repeated ear, respiratory infections
- Retinal degeneration, corneal blurriness
- Hepatosplenomegaly
- Hernias (umbilical, inguinal)
- Rib, hip, pelvis, vertebral abnormalities
- Stiff joints, claw-like hands
- Long bones thicken
- Thickened skin, short neck

DIAGNOSIS

DIAGNOSTIC IMAGING

X-ray

- Enlargement of skull, frontal bulging
- Lumbar, thoracic vertebral hypoplasia
- Pelvis hypoplasia, small femoral heads
- Metacarpals narrow proximally, widen distally

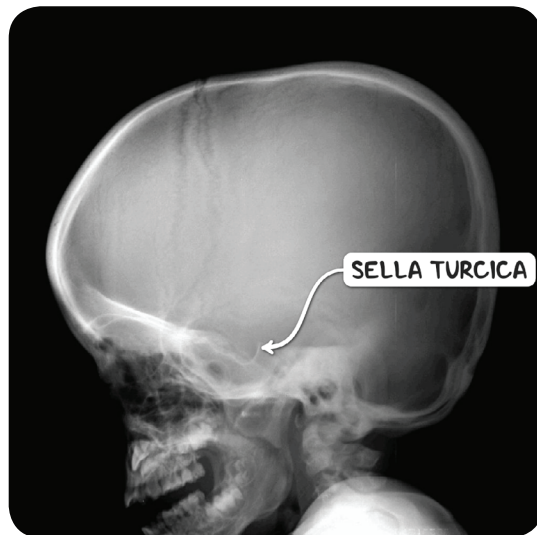


Figure 50.1 An X-ray image of the head of an infant with Hurler syndrome, showing a J-shaped sella turcica.

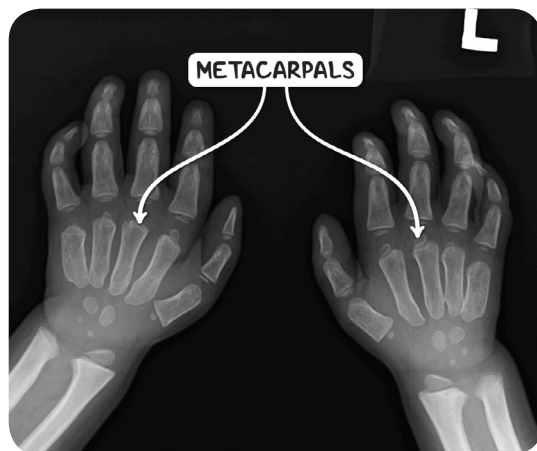


Figure 50.2 X-ray image of the hands of an infant with Hurler syndrome. The metacarpals are pointed at the proximal ends.

LAB RESULTS

- Enzyme activity in fibroblasts
 - ↓ alpha-L iduronidase
- ↑ heparan sulfate

OTHER DIAGNOSTICS

- Physical examination
 - Characteristic findings

TREATMENT

SURGERY

- Hand, foot abnormalities

OTHER INTERVENTIONS

- No definitive cure
- Address complications
- Recombinant human alpha-L-iduronidase
 - Laronidase (replaces missing enzyme)
- Bone marrow transplant